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Synthesis, Antimicrobial Activity, and Molecular Docking of Phenylcarbamate Derivatives Containing a Heterocyclic Fragment

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Abstract—The condensation of *o*-phenylenediamine with 2- and 4-aminobenzoic acids in 65% polyphosphoric acid at 180–190°C for 4 h or in boiling *o*-xylene in the presence of tetrabutoxytitanium gave 2-(2 or 4-aminophenyl)-1*H*-benzimidazoles, and acylation of the latter with methyl chloroformate in the presence of triethylamine afforded the corresponding benzimidazoles containing a carbamate moiety. The condensation of *o*-phenylenediamine and 4-nitrobenzene-1,2-diamine with glycolic acid in 70–75% polyphosphoric acid at 130°C for 4 h produced 81% of 1*H*-benzimidazol-2-ylmethanol and 84% of 5-nitro-1*H*-benzaimidazol-2-ylmethanol which were reacted with phenyl isocyanate in tetrahydrofuran at 27–30°C for 3.5 h to obtain the corresponding benzimidazol-2-ylmethyl phenylcarbamates in 84–86% yields. With the goal of finding most promising antimicrobial agents, the synthesized 2-substituted benzimidazole derivatives, as well as previously reported carbamate derivatives of pyridazine and *N*-allyl derivatives of 2-(morpholin-4-yl)ethyl and 2-(pyridin-2-yl)ethyl phenylcarbamates, were subjected to molecular docking study using glucosamine-6-phosphate synthase as the target protein.

Keywords: carbamate derivatives of benzimidazole and pyridazine, *N*-allyl derivatives of 2-(morpholin-4-yl)-ethyl and 2-(pyridin-2-yl)ethyl phenylcarbamates, molecular docking, glucosamine-6-phosphate synthase, antimicrobial activity

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INTRODUCTION

Currently, the molecular docking technique has found wide application in the field of drug research and development. This method simulates molecular interactions and predicts binding mode and affinity between a ligand and receptor. Screening of potential pharmacophores with the use of compound databases not only serves as a cost-reducing factor but also favors better prediction of the action of a supposed drug and understanding molecular mechanism of reactions, since this technology processes numerous biological data via optimization of the estimation function and modernization of the corresponding search algorithms [1, 2]. The screening-based approach provides more effective synthesis and pharmacological testing of potential medicines.

The present study deals with the synthesis of phenylcarbamate derivatives containing benzimidazole, pyridazine, morpholine, and pyridine fragments, as well as with molecular docking of the synthesized compounds into the active site of the enzyme glucosamine-6-phosphate synthase, with the goal of finding out derivatives with potential antimicrobial (antifungal) activity that are most promising for further studies.

Functionally substituted nitrogen-containing heterocyclic compounds exhibit a broad spectrum of biological activity due to their efficient binding to the

enzyme active site. Benzimidazole derivatives possess various biological activities, including antitumor [3], antifungal and antiviral [4], antimicrobial [5, 6], anti-inflammatory, analgesic [7], and antitubercular activities [8]. They are also used as 5-HT_{2A} antagonists [9], antidiabetic, antiviral, neurological, endocrinological, and ophthalmological agents [10], as well as in veterinary [11]. Some benzimidazole derivatives are used for the preparation of superstrong heat-resistant polymeric materials [12].

Compounds possessing valuable pharmacological properties were also found among heterocyclic compounds containing pyridazine, pyridine, and morpholine fragments. Nowadays, pyridazine derivatives are of great interest due to the broad spectrum of their activities as antithrombotic, antisecretory, antiulcer, analgesic, anti-inflammatory, and chemotherapeutic agents, as well as CNS stimulants [13–18]. Compounds containing a pyridazine fragment have found application in clinical practice; examples are the cardiotonic agent levosimendan and the peptide antibiotic antrimycin [19].

GlaxoSmithKline Pharmaceuticals Ltd. has recently recognized pyridazine ring one of the best available heterocycles for drug development [20]; in addition, interactions of pyridazine derivatives as ligands with various protein receptors have been reported [21–23]. Pyridine ring is a structural unit of many natural and synthetic compounds [24–28]. For example, omeprazole and netupitant are marketed drugs containing a pyridine ring. During the past decade, several pyridine derivatives, such as abemaciclib, lorlatinib, apalutamide, and ivosidenib, have been approved for therapy of some cancers [29]. Substituted morpholines are known to exhibit analgesic, anti-inflammatory, antioxidant, antihyperlipidemic, antimicrobial, anti-neurodegenerative, and anticancer activities [30, 31].

Given the above stated facts, the synthesis of new phenylcarbamate derivatives with a nitrogen-containing heterocyclic fragment is of great practical interest from the viewpoint of searching for new pharmaceuticals for further study.

RESULTS AND DISCUSSION

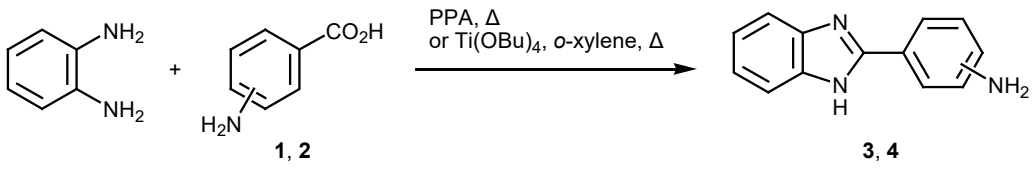
1*H*-Benzimidazole derivatives are commonly synthesized by the condensation of *N*-monoacyl-*o*-phenylenediamines [32] and intramolecular oxidative cyclization of Schiff bases obtained from *o*-phenylenediamine and aldehydes [33–35]. Depending on the nature of the reagents involved in the formation of the heterocycle, there are also specific one- and multicomponent methods for benzimidazole ring closure. The cyclizations are performed in the presence of various catalysts, such as 4 N aqueous HCl, polyphosphoric acid (PPA), sulfuric, boric, and metaboric acids, anhydrous phosphoric acid, ammonium acetate, and some others [36–40]. The use of polyphosphate ester (or ethyl metaphosphate) in the synthesis of 2-substituted benzimidazoles was also reported [41].

According to [42], the condensation of 2-aminobenzoic acid (**1**) with *o*-phenylenediamine in the presence of tetrabutoxytitanium in boiling *o*-xylene produced the corresponding benzimidazole derivative **2** [42]. Some benzimidazole derivatives containing a carbamate moiety (e.g., mebendazole, carbendazim, albendazole, and fenbendazole) are already used in clinical practice as anthelminthic agents with a broad spectrum of action [43].

We found that heating a mixture *o*-phenylenediamine and 1.5 equiv of 2(4)-aminobenzoic acid **1** or **2** in 60% polyphosphoric acid with stirring at 180–190°C for 4 h led to the formation of the corresponding 2-(aminoaryl)-1*H*-benzimidazoles **3** and **4** in 64–66% yields (Scheme 1). When a mixture of *o*-phenylenediamine and aminobenzoic acid **1** or **2** at a ratio of 2:1 in the presence of tetrabutoxytitanium was heated in boiling xylene for 2 h, the yield of **3** and **4** was lower, 51–52%. The structure of compounds **3** and **4** was confirmed by IR and ^{1}H NMR spectra and elemental analyses.

The acylation of compounds **3** and **4** at the primary amino group with methyl chloroformate in THF in the presence of triethylamine afforded 95–97% of the corresponding carbamates **5** and **6** (Scheme 2).

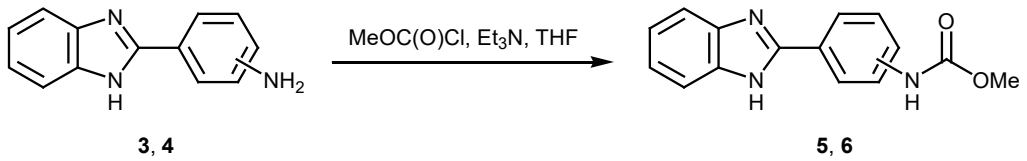
Scheme 1.



1, **2** **3**, **4**

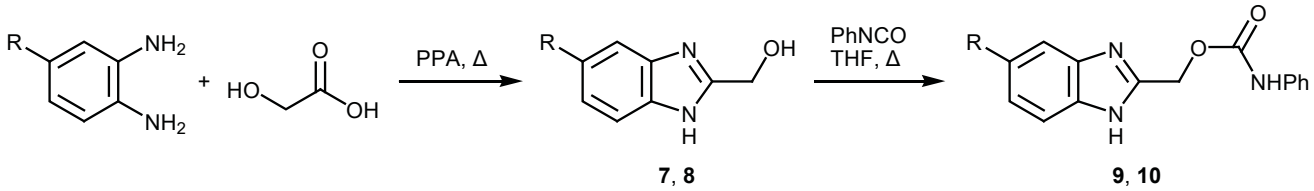
1, **2**, 2-NH_2; **3**, **4**, 4-NH_2.

Scheme 2.



5, 2-$NHCO_2Me$; **6**, 4-$NHCO_2Me$.

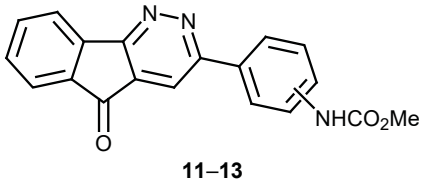
Scheme 3.



7, **9**, R = H; **8**, **10**, R = NO_2.

To further develop our study, *o*-phenylenediamine and 4-nitro-*o*-phenylenediamine were reacted with glycolic acid on heating in 70–75% polyphosphoric acid at 130°C for 4 h. As a result, we obtained 2-(hydroxymethyl)benzimidazole **7** [36] in 81% yield and 5-nitro-2-(hydroxymethyl)benzimidazole **8** [44] in 84% yield. The reactions of **7** and **8** with phenyl isocyanate in THF at 27–30°C for 3.5 h gave benzimidazole derivatives **9** and **10** in 84–86% yields (Scheme 3). The structure of **9** and **10** was confirmed by IR and ^1H NMR spectra.

Pyridazine derivatives **11**–**13** were synthesized by reacting methyl (acetylphenyl)carbamates with ninhydrin in the presence of acetic acid, followed by treatment with hydrazine hydrate in acetonitrile [45]. 2-(Morpholin-4-yl)ethyl) and 2-(pyridin-2-yl)ethyl phenyl(prop-2-en-1-yl)carbamates **14** and **15** were prepared by alkylation of the corresponding phenylcarbamates with allyl bromide under phase-transfer catalysis [46].



11, 2-$NHCO_2Me$; **12**, 3-$NHCO_2Me$; **13**, 4-$NHCO_2Me$.

As noted above, molecular docking is an important tool for predicting biological activity, as it provides the possibility of calculating the binding energy of the complex formed by a compound with the active site of enzyme responsible for undesirable reactions. The lower the binding energy, the stronger the complex. The formation of a strong complex makes the enzyme inactive, thus preventing undesirable biochemical reaction.

For the molecular docking study, we selected glucosamine-6-phosphate synthase (GlcN-6-P synthase) which is produced in all living species. The inhibition of this enzyme exerts various positive effects. First of all, it plays a key role in the formation of the cell wall of microorganisms, such as bacteria, protozoa, and fungi; therefore, even short-term inhibition of this enzyme leads to a selective antibacterial and antifungal effect, while such inhibition is not harmful to the human body whose cell membranes have a fundamentally different structure. Consequently, compounds capable of forming a strong complex with GlcN-6-P synthase can be considered potential antibacterial, antimicrobial, and antifungal agents [47].

Thus, molecular docking makes it possible to identify promising antibacterial, antimicrobial, and antifungal properties of compounds whose activity originates from the inhibition of glucosamine-6-phosphate synthase. The enzyme contains several domains involved in different stages of the catalytic reaction, so that ligands can bind to different fragments of the protein. Analysis of literature data showed that nitrogen-containing heterocyclic molecules can form strong complexes with that part of the enzyme, which is responsible for the second stage of the catalytic reaction (ISOM domain) (Fig. 1) [48–50]; therefore, it is reasonable to perform molecular docking into the active site located in the ISOM domain.

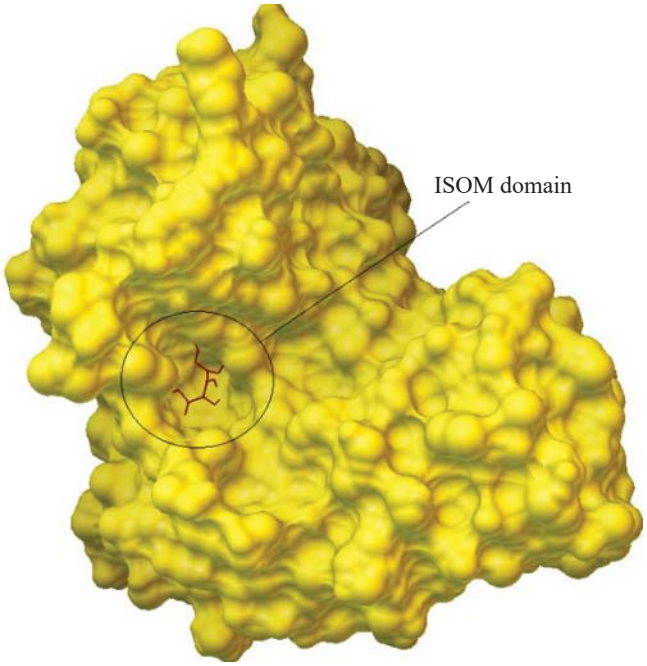


Fig. 1. ISOM domain of glucosamine-6-phosphate synthase.

The molecular docking of compounds **6** and **9**–**14** was performed using AutoDockTools (ADT) version 1.5.6 and AutoDock version 4.2.5.1 [51, 52]. The protein structure (as a complex with glucosamine-6-phosphate) was retrieved from the Protein Data Bank (PDB ID: 2VF5). Preliminarily, all water molecules, the ligand, and counterions were removed from the structure, and the file was converted into the PDBQT format with addition of missing hydrogen atoms and calculated charges. The structures of all ligands were optimized by the MM2 method implemented in Chem3D software [53], and the obtained coordinates of atoms of the ligand molecules were transferred to the PDBQT format for further calculations.

The calculated conformations of the ligand–protein complexes were compared by binding energies (E_{bind}); in addition, the total number of conformations of one cluster, where the root-mean-square deviation (RMSD) of the ligand position differs by no more than 2 Å, was estimated, so that the complexes had close energy characteristics. The binding energy (E_{bind}) was calculated by the formula:

$$\Delta E_{bind} = \Delta E_{vdW} + \Delta E_{elec} + \Delta E_{Hbond} + \Delta E_{desolv} + \Delta E_{torsion},$$

where ΔE_{vdW} is the energy of intermolecular van der Waals interactions, ΔE_{elec} is the energy of electrostatic interactions, ΔE_{desolv} is the desolvation energy, and $\Delta E_{torsion}$ is the torsional strain energy.

In all cases, the characteristics of the complexes were calculated for the conformation with the least binding energy in the cluster with the maximum number of conformations, where the ligand positions differed by no more than 2Å. The lowest protein–ligand binding energies were obtained for compounds

Table 1. Hydrophobic hydrogen-bonding interactions between the ligand and receptor

Compound no.	E_{bind}, kcal/mol	Hydrophobic interactions	Hydrogen bonds
6	–8.03	Ala602, Leu601, Val605, Gln408, Ser401, Gln348, Ser303, Thr302	–
9	–8.68	Ser604, Lys603, Cys300, Thr302, Ser303, Gln348, Ser349, Glu488, Thr352	Ser604
10	–10.27	Val605, Ser604, Lys603, Ala602, Leu601, Gln408, Ser401, Val399, Thr352, Gln348, Ser303, Thr302	Ser604
11	–9.71	Val605, Ala602, Leu601, Gln408, Phe405, Ser401, Gln348, Ser303, Thr302	–
12	–10.46	Val605, Ser604, Ala602, Leu601, Gln408, Ser401, Ser349, Gln348, Ser303, Thr302	–
13	–10.36	Val605, Ser604, Ala602, Leu601, Gln408, Ala404, Ser401, Gln348, Ser303	Gln348
14	–7.81	Ile131, Lys143, Leu139, Gln142, Leu300, Gly303, Ile304, Gly307, Thr311	–
15	–8.98	Ala200, Leu204, Leu305, Glu308, Gln309, Thr311, Ser312, Thr315, Phe463, Gly472, Phe475, Ala476	–

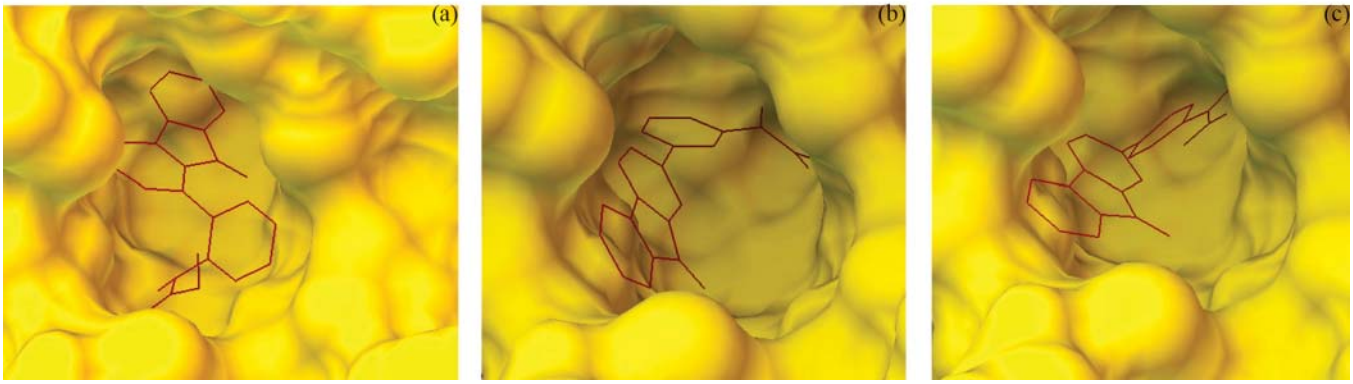


Fig. 2. Orientations of ligands (a) **11**, (b) **12**, and (c) **13** in the active site of glucosamine-6-phosphate synthase (PDB ID: 2VF5).

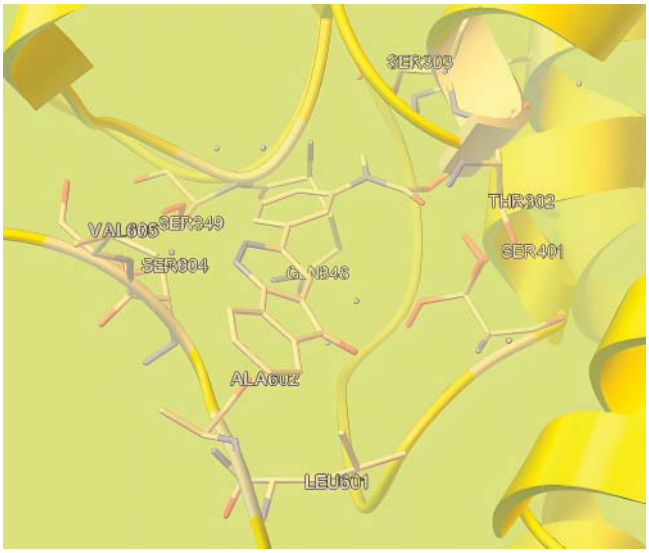


Fig. 3. Amino acid residues in the active site of glucosamine-6-phosphate synthase, involved in hydrophobic interactions with compound **12**.

11–**13**, which can be explained by the large number of hydrophobic interactions between the heterocyclic fragment and hydrophobic amino acid residues (Table 1).

In addition, hydrogen bonding between the $NHCO_2Me$ fragment of compounds **11** and **13** and some amino acid residues was observed; however, this factor is not crucial. The position of the $NHCO_2Me$ group in the phenyl ring of **11**–**13** is important, and it affected the efficiency of the interaction with the enzyme (Fig. 2). When the carbamate functionality occupies the *meta* or *para* position, the resulting complexes have lower energy, and the ligand orientations therein are similar; however, in the case of compound **12**, the number of possible hydrophobic interactions is greater, so that the binding energy is slightly lower. The presence of the $NHCO_2Me$ group at the *ortho* position radically changes orientation of the ligand, which impairs energy characteristics of the complex.

Figure 3 shows the docking pose of compound **12** in the active site of glucosamine-6-phosphate synthase and amino acid residues involved in hydrophobic interactions with the ligand.

The low binding energy was also found for ligand **10** bearing a nitro group in the aromatic fragment. Importantly, the binding energy calculated for ligand **9** which, unlike **10**, contains no nitro group, has a higher value. The reason is that the number of hydrophobic interactions in the complex with ligand **9** is lower. In particular, this complex lacks hydrophobic interactions with the amino acid residues Val605, Ala602, Leu601, Gln408, Ser401, and Val399, which are typical of ligand **10** (Fig. 4).

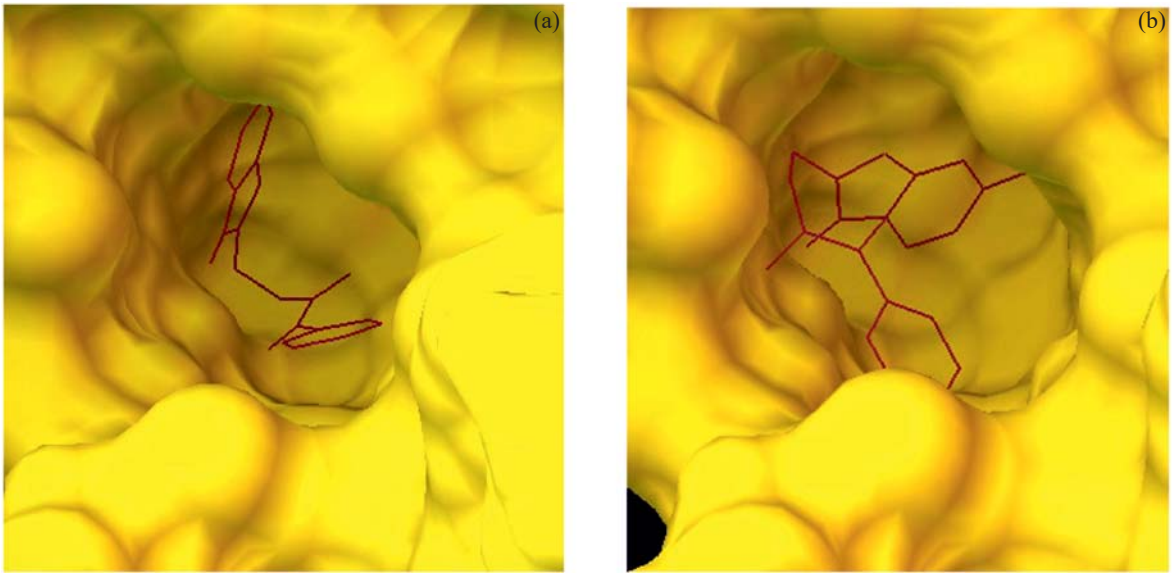


Fig. 4. Orientations of ligands (a) **10** and (b) **11** in the active site of glucosamine-6-phosphate synthase (PDB ID: 2VF5).

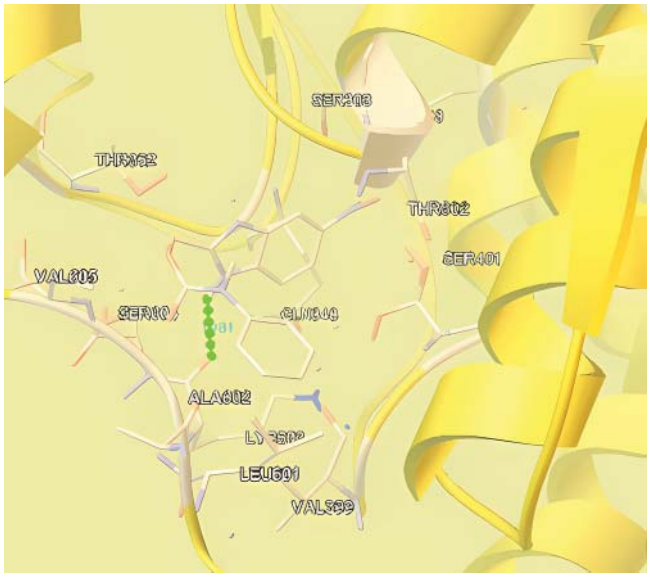


Fig. 5. Amino acid residues in the active site of glucosamine-6-phosphate synthase, involved in hydrophobic interactions with compound **10**.

Figure 5 shows amino acid residues involved in hydrophobic interactions of compound **10** with glucosamine-6-phosphate synthase.

The obtained data suggest that the complexation between the enzyme and benzimidazole derivative **10** and pyridazines **11**–**13** is the most favorable. The molecular docking results for compounds **6**, **9**, and **10**–**15** were in agreement the results of studying their antimicrobial activity against *S. Pneumoniae*, *S. aureus* 209 P, *P. aeruginosa* 165, and *E. coli* DSM 30083 strains, which was determined by the agar diffusion method [54] (Table 2). As seen in Table 2, pyridazine derivatives **11**–**13** exhibited the highest antimicrobial activity.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DRX 500 spectrometer (USA) at 500 MHz using DMSO-d_6 as a solvent. The IR spectra were recorded in the range of 4000–400 cm^{-1} on an InfraLUM FT-02 FTIR spectrometer (Russia) from samples prepared as KBr discs. The purity of the isolated compounds was

Table 2. Antimicrobial activity of compounds **6** and **9**–**15**

Compound no.	Inhibition zone diameter,[a] mm			
	S. pneumoniae	*S. aureus* 209P	*P. aeruginosa* 165	*E. coli* DSM 30083
6	ND	7±1.2	ND	9±0.5
9	ND	9±2.0	ND	10±1.4
10	ND	15±2.3	ND	13±1.7
11	27±1.7	30±1.3	25±1.5	22±1.6
12	24±1.4	34±1.8	31±1.5	26±1.4
13	20±1.5	27±0.8	18±0.7	15±0.3
14	ND	16±1.2	ND	14±0.9
15	ND	18±2.1	ND	17±1.3
Gentamycin sulfate	40±0.6	42±1.2	22±0.1	35±0.4

[a] "ND" stands for "not determined."

checked by TLC on Silufol UV-254 plates (Chemapol, Czechia); spots were visualized by treatment with iodine vapor. Elemental analysis was performed with a Perkin Elmer 2400 Series II analyzer (USA). Commercially available reagents from Aldrich and Alfa Aesar (USA) were used. Compounds **7** and **8** were synthesized according to the literature procedure [44].

2-(1*H*-Benzimidazol-2-yl)aniline (3). *a*. A mixture of 4.11 g (30 mmol) of 2-aminobenzoic acid and 2.16 g (20 mmol) of *o*-phenylenediamine in 50 mL of 65% polyphosphoric acid was heated at 180–200°C for 4 h with efficient stirring. The mixture was cooled to 40–50°C, poured onto 50 g of crushed ice, and neutralized with 25% aqueous ammonia. The precipitate was filtered off, washed with 10% aqueous sodium hydroxide, dried in air, and recrystallized from ethanol. Yield 2.68 g (64%), mp 211–213°C; published data [42]: mp 210–213°C. IR spectrum, ν, cm^{-1}: 3433 (NH), 3348, 3215 (NH_2), 1632 (C=N), 1605, 1575 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 5.54 s (2H, NH_2), 6.67 t (2H, H_{arom}, J = 8.7 Hz), 6.93–6.98 m (2H, H_{arom}), 7.20 t (1H, H_{arom}, J = 7.7 Hz), 7.56 d (2H, J = 8.7 Hz), 8.28 d (1H, H_{arom}, J = 7.7 Hz), 12.43 s (1H, NH). Found, %: C 74.48; H 5.14; N 19.75. $C_{13}H_{11}N_3$. Calculated, %: C 74.64; H 5.26; N 20.10.

b. Compound **3** was also obtained as described in [42] by heating a mixture of 1.123 g (8.2 mmol) of 2-aminobenzoic acid, 1.77 g (16.4 mmol) of *o*-phenylenediamine, and 0.544 g (1.6 mmol) of $Ti(OBu)_4$ in 40 mL of anhydrous *o*-xylene under reflux for 2 h. The solvent was removed under reduced pressure, the residue was washed with 25% aqueous ammonia (5 mL) and warm water (300 mL), and treated with boiling toluene (40 mL). The solution was filtered from TiO_2 and dried over sodium sulfate, and the solvent was evaporated. Yield 0.89 g (52%), mp 210–213°C.

4-(1*H*-Benzimidazol-2-yl)aniline (4) was synthesized as described above for compound **3** (method *a*) from 4.11 g (30 mmol) of 4-aminobenzoic acid and 2.16 g (20 mmol) of *o*-phenylenediamine. Yield 2.76 g (66%), mp 235–237°C [51]. IR spectrum, ν, cm^{-1}: 3430 (NH), 3350, 3216 (NH_2), 1630 (C=N), 1605, 1570 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 5.56 s (2H, NH_2), 6.64 d (2H, H_{arom}, J = 8.4 Hz), 7.05–7.10 m (2H, H_{arom}), 7.43–7.49 m (2H, H_{arom}), 7.80 d (2H, J = 8.4 Hz), 12.44 s (1H, NH). Found, %: C 74.34; H 5.25; N 19.83. $C_{13}H_{11}N_3$. Calculated, %: C 74.64; H 5.26; N 20.10.

Compound **4** was also synthesized according to method *b*. Yield 0.87 g (51%), mp 234–236°C.

Methyl [2-(1*H*-benzimidazol-2-yl)phenyl]carbamate (5). A mixture of 2.09 g (10 mmol) of 2-(1*H*-benzimidazol-2-yl)aniline (**3**) and 0.5 mL of triethylamine in 10 mL of anhydrous THF was cooled to 0°C, and 0.79 mL (10.2 mmol) of methyl chloroformate was added dropwise with vigorous stirring over a period of 0.5 h. The mixture was stirred at room temperature for 2 h and poured onto crushed ice (50 g), and the crystalline solid was filtered off, dried in air, and recrystallized from ethanol. Yield 2.54 g (95%), colorless crystals, mp 195–196°C. IR spectrum, ν, cm^{-1}: 3430, 3320 (NH), 1710 (C=O), 1635 (C=N), 1608, 1570 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, $NHCO_2$**Me**), 5.73 t (2H, H_{arom}, J = 8.9 Hz),

7.32–7.39 m (2H, H_{arom}), 7.56 d (2H, H_{arom}, J = 8.9 Hz), 7.93 d (1H, J = 7.7 Hz), 8.54 d (1H, H_{arom}, J = 7.7 Hz), 9.59 s (1H, N**H**CO_2Me), 12.44 s (1H, NH). Found, %: C 67.13; H 4.67; N 15.59. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.42; H 4.87; N 15.73.

Methyl [4-(1*H*-benzimidazol-2-yl)phenyl]carbamate (6) was synthesized as described above for compound **5** from 2.09 g (10 mmol) of 4-(1*H*-benzimidazol-2-yl)aniline (**4**) and 0.79 mL (10.2 mmol) of methyl chloroformate. Yield 2.59 g (97%), colorless crystals, mp 250–253°C (from EtOH). IR spectrum, ν, cm^{-1}: 3427, 3315 (NH), 1710 (C=O), 1635 (C=N), 1610, 1575 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO$_2$**Me**), 5.73 t (2H, H_{arom}, J = 8.9 Hz), 7.12 d (2H, H_{arom}, J = 8.5 Hz), 7.56 d (2H, H_{arom}, J = 8.9 Hz), 8.55 d (2H, H_{arom}, J = 8.5 Hz), 9.55 s (1H, N**H**CO_2Me), 12.43 s (1H, NH). Found, %: C 67.24; H 4.55; N 15.70. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.42; H 4.87; N 15.73.

(1*H*-Benzimidazol-2-yl)methyl phenylcarbamate (9). Phenyl isocyanate, 1.49 mL (13.7 mmol), was added dropwise to a solution of 2 g (13.5 mmol) of (1*H*-benzimidazol-2-yl)methanol in 10 mL of anhydrous THF, and the mixture was stirred at 27–30°C for 3.5 h. The mixture was poured onto crushed ice (50 g), and the solid product was filtered off, washed with water (20 mL), dried in air, and recrystallized from ethanol. Yield 3.03 g (84%), colorless crystals, mp 220–223°C (from EtOH). IR spectrum, ν, cm^{-1}: 3433, 3330 (NH), 1710 (C=O), 1630 (C=N), 1610, 1570, 1565 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 5.25 s (2H, CH_2), 7.02–7.07 m (1H, H_{arom}), 7.15–7.24 m (4H, H_{arom}), 7.34 d (2H, H_{arom}, J = 7.9 Hz), 7.42 d (2H, J = 8.9 Hz), 9.54 s (1H, NH), 12.45 s (1H, NH). Found, %: C 67.21; H 4.56; N 15.39. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.42; H 4.87; N 15.73.

(5-Nitro-1*H*-benzimidazol-2-yl)methyl phenylcarbamate (10) was synthesized as described above for compound **9** from 2.6 g (13.5 mmol) of (5-nitro-1*H*-benzimidazol-2-yl)methanol and 1.49 mL (13.7 mmol) of phenyl isocyanate. Yield 3.6 g (86%), colorless crystals, mp 230–233°C (from EtOH). IR spectrum, ν, cm^{-1}: 3430, 3330 (NH), 1710 (C=O), 1630 (C=N), 1612, 1575, 1562 (C=C_{arom}), 1520, 1350 (NO_2). ^{1}H NMR spectrum, δ, ppm: 5.24 s (2H, CH_2), 7.02–7.07 m (1H, H_{arom}), 7.19–7.27 m (2H, H_{arom}), 7.36 d (2H, H_{arom}, J = 8.8 Hz), 7.86 d (1H, H_{arom}, J = 8.9 Hz), 8.01 d (1H, H_{arom}, J = 8.9 Hz), 8.53 s (1H, H_{arom}), 9.56 s (1H, NH), 12.44 s (1H, NH). Found, %: C 57.72; H 3.61; N 17.84. $C_{15}H_{12}N_4O_4$. Calculated, %: C 57.69; H 3.85; N 17.95.

Antimicrobial activity. The in vitro antimicrobial activity of the synthesized compounds was determined by the agar diffusion method using Mueller–Hinton agar preliminarily inoculated with the test cultures containing 10^5 CFU per milliliter of saline. The compounds to be tested were dissolved in DMSO to a concentration of 1 mg/mL, and 25 μL of the solution was added to each well of a microplate. The microplates were incubated at 37±1°C, and the diameter of the zone of bacterial growth inhibition around the wells was measured with an accuracy of ±1 mm [55]. A solution of gentamycin sulfate in DMSO with a concentration of 40 mg/mL was used as reference. The results of measurements were statistically processed.

CONCLUSIONS

2-Substituted benzimidazoles with a carbamate functionality have been synthesized by the condensation of *o*-phenylenediamine with 2(4)-aminobenzoic acids in polyphosphoric acid, followed by acylation of the primary amino group with methyl chloroformate in the presence of triethylamine in THF, as well as by the condensation of *o*-phenylenediamine and 4-nitrobenzene-1,2-diamine with glycolic acid in polyphosphoric acid, followed treatment of the resulting (1*H*-benzimidazol-2-yl)methanols with phenyl isocyanate in THF. Molecular docking study of 2-substituted benzimidazoles and previously synthesized pyridazine derivatives with a carbamate fragment and 2-(morpholin-4-yl)ethyl and 2-(pyridin-2-yl)ethyl phenyl(prop-2-en-1-yl)carbamates against glucosamine-6-phosphate synthase has revealed most promising compounds in terms of antimicrobial activity. Among the tested compounds, pyridazine derivatives **11**–**13** showed the highest in vitro antimicrobial activity.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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